AM-100171

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	: 10/758,187	Confirmation No.: 5603
Applicant	: Considine et al	
Filed	: January 15, 2004	
Patent No.	: 7,126,025	
Issued	: October 24, 2006	
TC/A.U.	: 1621	
Examiner	: Davis, Brian J	
Customer No.	: 38199	
Title	: SYNTHESIS OF 4-(AMINO)-2-BUTENOYL CHLORIDES AND THEIR USE IN THE PREPARATION OF 3-CYANO QUINOLINES	

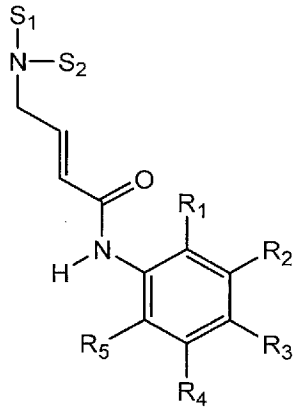
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

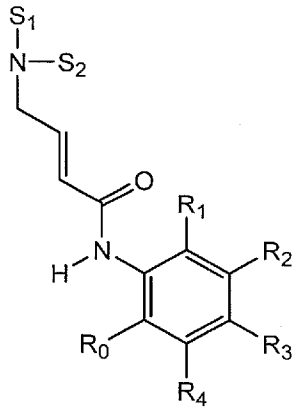
REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 35 USC SECTION 254

The following errors were found in the above-identified patent:

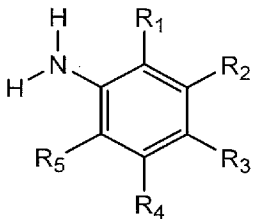
(1) Col. 3, lines 20-34 delete the following structure:



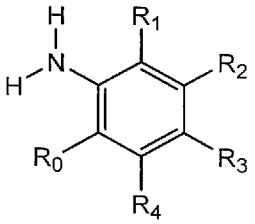
and insert the following structure:



(2) Col. 4, lines 5-14, delete the following structure:



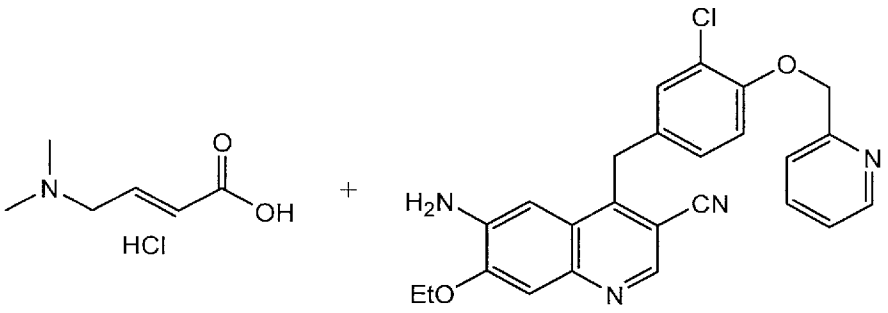
and insert the following structure:



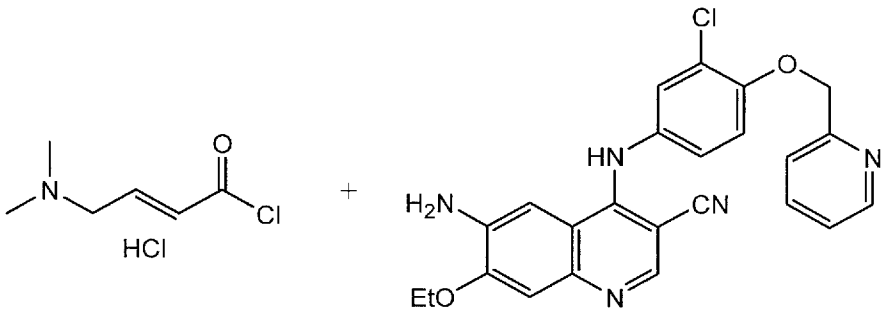
(3) Col. 4, line 59, replace " "X" " with -- "X'" -- ;

(4) Col. 6, line 1, replace " R'''SO_2NH radical, where R''' " with -- R'''SO_2NH radical, where R''' -- ;

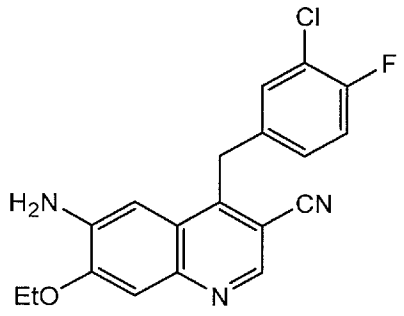
(5) Cols. 13-14, lines 15-35, delete the following:



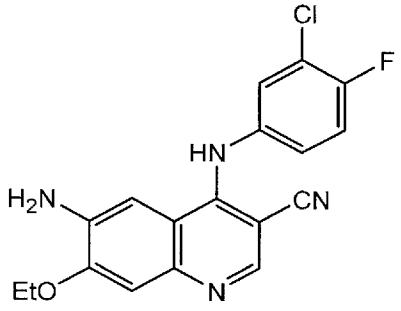
and insert the following:



(6) Cols.15-16, lines 15-35, delete the following structure:

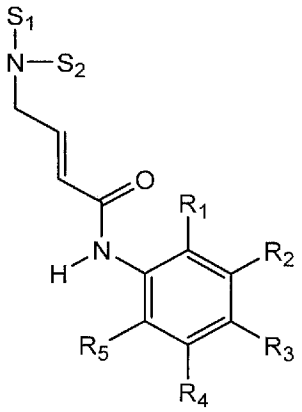


and insert the following structure:

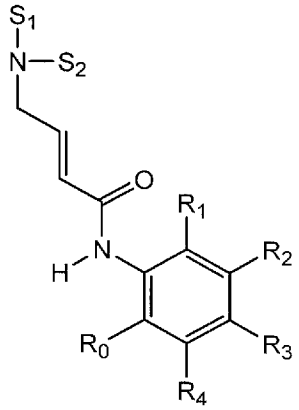


(7) Col. 20, Line 55, delete the second occurrence of "4-Dimethylaminocrotonic acid

(8) Claim 5, Col. 23, lines 45-60, delete the following structure:



and insert the following structure:



It is requested that a Certificate of Correction be issued to correct the above error in accordance with the enclosed Form PTO 1050, which is submitted herewith.

These errors are typographical in nature and make no substantive changes. All errors were made by the USPTO, no fee is due for correction of these errors.

Enclosed for each correction is a photocopy of the original specification page with the relevant words or phrases highlighted in blue and the corresponding original patent with errors marked in red. These documents will support the USPTO errors.

The Director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,

HOWSON & HOWSON LLP

Attorneys for the Applicants

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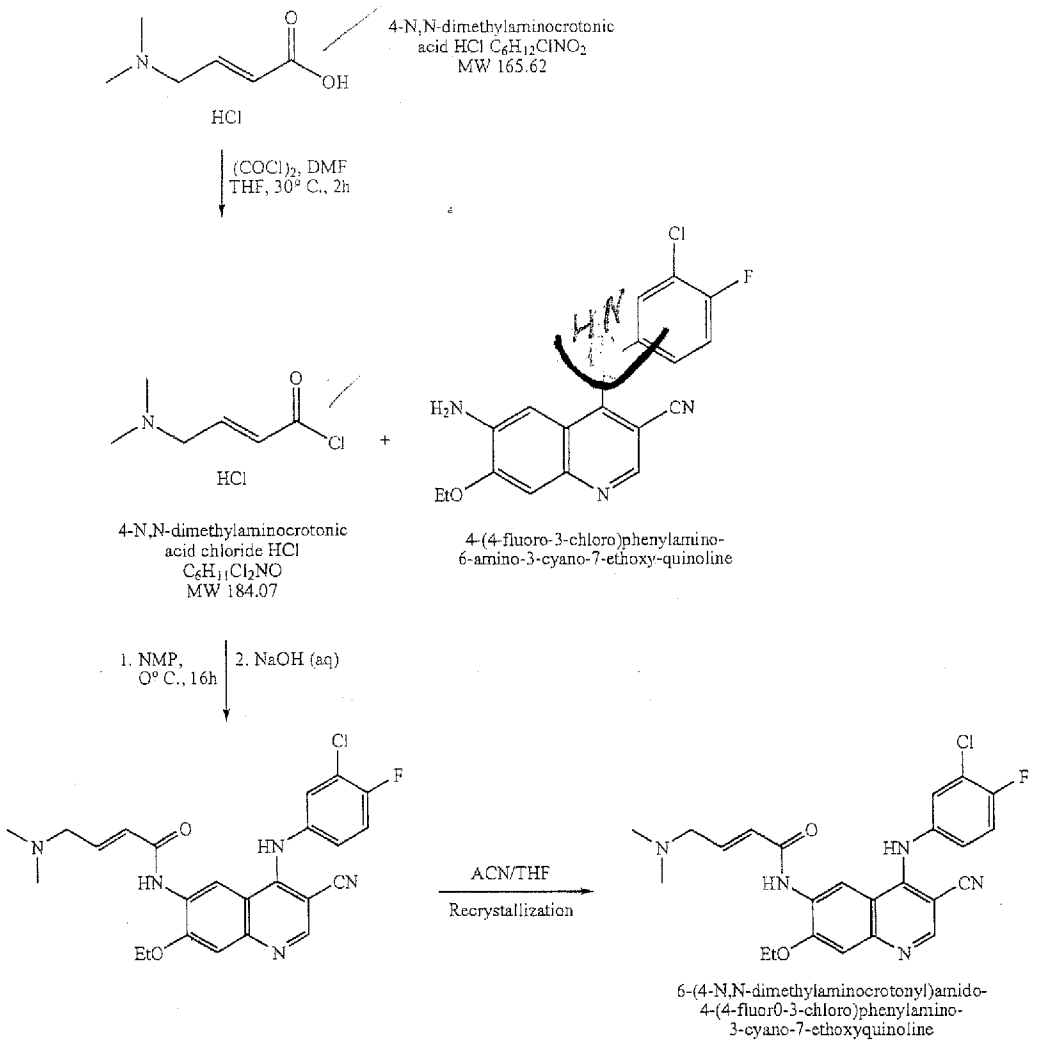
Reaction Scheme Example 3:



4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]amide

4-(Dimethylamino)-2-butenoyl chloride hydrochloride

A 1 L multi-neck flask equipped with agitator, thermometer, addition funnel, and nitrogen protection is charged with acetonitrile (0.67 kg, 0.85 L) followed by adding dimethylformamide (0.00086 kg, 0.91 mL, d=0.944 g/mL). At ambient temperature, is added 4-dimethylaminocrotonic acid hydrochloride (0.0709 kg) and the mixture stirred until homogeneous. Cool the reaction mixture to (0–10° C.) and add oxalyl chloride (0.0473 kg, 0.0325 L, d=1.45 g/mL) dropwise over (20 minutes) at (0–10° C.) followed by a rinse with acetonitrile (0.02 kg, 0.03 L). The temperature (0–10° C.) is maintained for about (20 minutes). The temperature of the reaction mixture is adjusted to (22–26° C.) over (20 minutes) and maintained over (2 hours). The temperature of reaction mixture is adjusted to (40–45° C.) and held for about (5 minutes). Cool the light suspension to about (20–25° C.) and check for reaction completion by high-pressure liquid chromatography (HPLC). The reaction is complete when there is ≦15% of the starting material (4-dimethylaminocrotonic acid hydrochloride) present and/or ≦2% of oxalyl chloride (detected as the dimethyl oxalate).

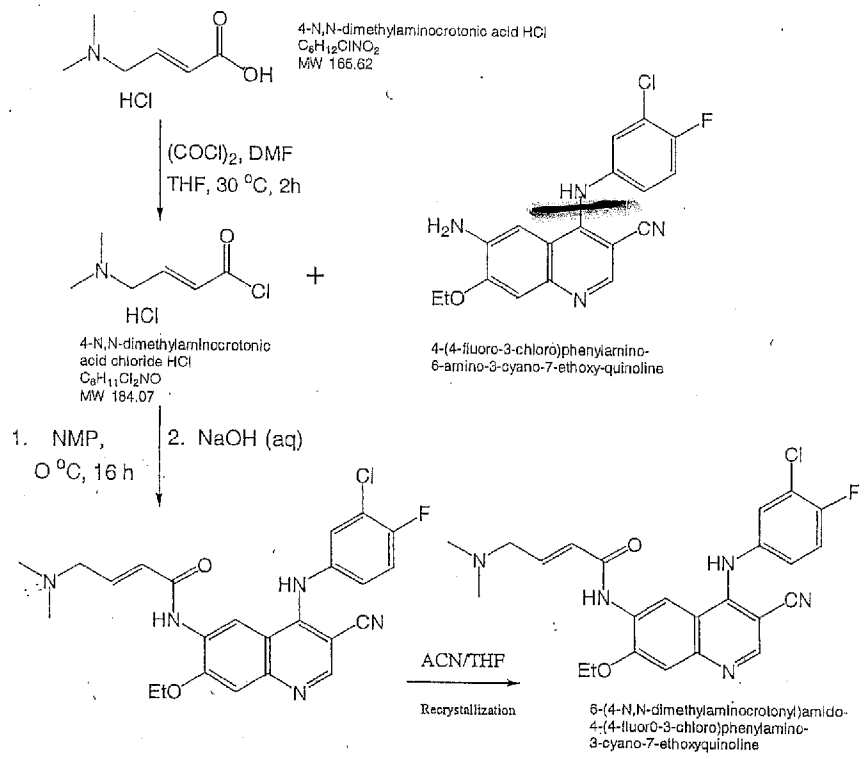
4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide (Crude)

A 3 L multi-neck flask equipped with agitator, thermometer, dip tube, and nitrogen protection is charged N-methyl pyrrolidinone (0.77 kg, 0.75 L, d=1.033 g/mL). At ambient temperature is added 4-[3-chloro-4-fluorophenyl]amino-6-amino-3-cyano-7-ethoxy quinoline (0.0748 kg). The reaction mixture is heated to 40–45° C. and maintained for about (15 minutes). The reaction mixture is cooled to (0–10° C.) and the light suspension of 4-(dimethylamino)-2-butenoyl chloride hydrochloride in CH_3CN added via dip tube and positive nitrogen pressure, over (30–45 minutes) while maintaining the temperature (0–10° C.) for at least (2 hours). Reaction completion is monitored by HPLC. The reaction is complete when there is ≦2% of the starting material (4-[3-chloro-4-fluorophenyl]amino-6-amino-3-cyano-7-ethoxy quinoline) present. To a 12 L multi-neck flask equipped with agitator, thermometer, dip tube, and nitrogen protection is

ERROR (6)

acetonitrile:THF (1:5:1) and the solution cooled slowly to room temperature. The product is filtered and washed with acetonitrile:THF. The product is dried (50º C, 10 mm Hg, 24 hours) to 80-85% yield.

Reaction Scheme Example 3:



4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]amide

4-(dimethylamino)-2-butenoyl chloride hydrochloride

A 1 L multi-neck flask equipped with agitator, thermometer, addition funnel, and nitrogen protection is charged with acetonitrile (0.67 kg, 0.85 L) followed by adding dimethylformamide (0.00086 kg, 0.91 mL, d=0.944 g/mL). At ambient temperature, is added 4-dimethylaminocrotonic acid hydrochloride (0.0709 kg) and

ERRORS(1) & (2) & (3)

In one embodiment of the invention S_1 and S_2 are CH_3 or an acid addition salt thereof and the process for the preparation of the compound comprises:

(a) reacting but-2-enoic acid with chlorotrimethylsilane to obtain trimethylsilylcrotonate;

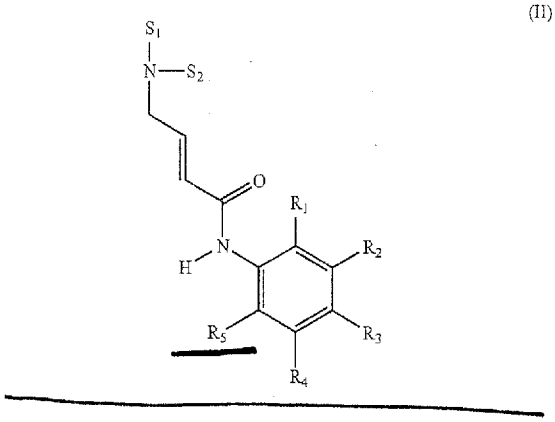
(b) brominating trimethylsilylcrotonate of step (a) with a brominating agent to obtain trimethylsilyl-4-bromocrotonate;

(c) reacting trimethylsilyl-4-bromocrotonate of step (b) or methyl or ethyl 4-bromocrotonate with dimethylamine to obtain 4-dimethylaminocrotonic acid; and

(d) isolating the compound of step (c) as a hydrochloride salt and chlorinating with a chlorinating agent to obtain the compound of of the invention wherein 1 wherein S_1 and S_2 are CH_3.

In another embodiment the invention provides a process for the preparation of a compound of Formula (II):

(II)



wherein

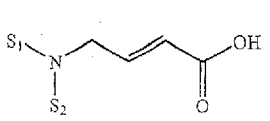
R_1, R_2, R_3, R_4, and R_0 are independently selected from the group consisting of —H, —CN, alkyl, alkoxy, vinyl, alkenyl, formyl, —CF_3, —CCl_3, halide, —C_6H_5, amide, acyl, ester, amino, thioalkoxy, phosphino, and combinations thereof;

or, taken together, R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_0, together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl or cycloheteroalkyl; and

S_1 and S_2 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, substituted or unsubstituted aryl, or S_1 and S_2 together with the nitrogen to which they are attached form a nitrogen containing heteroaryl, comprising:

(a) cooling a suspension of an acid addition salt of the compound of Formula (V);

(V)



wherein S_1 and S_2 are defined above;

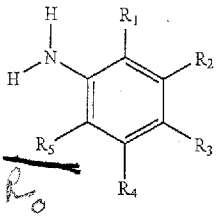
(b) adding a chlorinating agent to the suspension in step (a);

(c) warming and stirring the suspension in step (b) until the chlorinating agent is completely consumed;

(d) cooling the suspension in step (c);

(e) adding an aniline of formula (IV) dropwise to the suspension in step (d) until the concentration of the aniline is less than about 5%;

(IV)



wherein R_1, R_2, R_3, R_4 and R_0 are as defined above;

(f) adding an aqueous base to the suspension in step (e) to obtain a precipitate; and

(g) filtering and washing and drying the precipitate in step (f) to yield the compound of Formula (II).

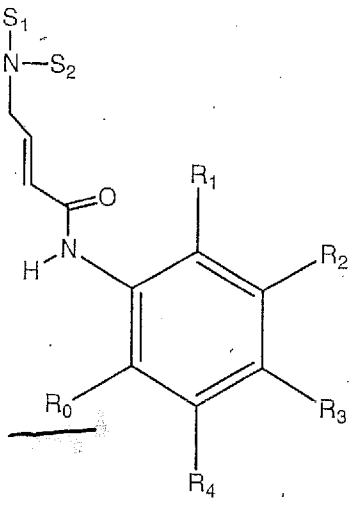
For purposes of this invention a heteroaryl comprises a heterocyclic ring system of one to three fused rings, in which at least one ring may have an aromatic character and contains 1 to 4 heteroatoms the same or different selected from the group consisting of S, N, and O. The remaining rings of the ring system may be fully unsaturated, partially saturated, or fully saturated. Each ring comprises three to ten members. Preferred heteroaryl groups are thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, pteridine, carbazole, phenanthridine, acridine, perimidine, phenanthroline, phenazine, phenothiazine, furazan, phenoxazineand pyrrolidine. The heteroaryl can be independently substituted at one or more positions. Preferred substituents are halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, acyl, aldehyde, ester, a cycloheteroalkyl, an aromatic or heteroaromatic moiety, —CN, or Y.

Cycloheteroalkyl as used herein refers to a 5 to 9 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms selected from N, N(C_1–C_6 alkyl), S or O. Preferred cycloheteroalkyl groups are oxolane, thiolane, oxazole, piperidine, piperazine and morpholine. The cycloheteroalkyl can be independently substituted at one or more positions. Preferred substituents are halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a cycloheteroalkyl, an aromatic or heteroaromatic moiety and —CN.

When the heteroaryl is substituted with Y, wherein Y is —NH, —O—, —S—, or —NR—, wherein R is an alkyl of 1–6 carbon atoms, at one position on the ring there is further substitution on the —NH, —O—, —S—, or —NR— with a (CH_2)n-X group. For purposes of this invention n is 0–1 and "X" is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atoms; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with substituents independently selected from the group consisting of halogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, azido, hydroxyalkyl of 1–6 carbon atoms, halomethyl, alkoxymethyl of 2–7 carbon

ERRORS (1)

In another embodiment the invention provides a process for the preparation of a compound of Formula (II):



(II)

wherein

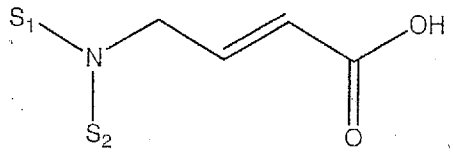
R_1, R_2, R_3, R_4, and R_0 are independently selected from the group consisting of –H, -CN, alkyl, alkoxy, vinyl, alkenyl, formyl, $-CF_3$, $-CCl_3$, halide, $-C_6H_5$, amide, acyl, ester, amino, thioalkoxy, phosphino, and combinations thereof;

or, taken together, R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_0, together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl or cycloheteroalkyl; and

S_1 and S_2 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, substituted or unsubstituted aryl, or S_1 and S_2 together with the nitrogen to which they are attached form a nitrogen containing heteroaryl, comprising:

(a) cooling a suspension of an acid addition salt of the compound of Formula (V);

ERROR (2)



(V)

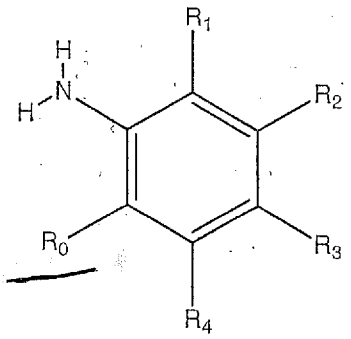
wherein S_1 and S_2 are defined above;

(b) adding a chlorinating agent to the suspension in step (a) ;

(c) warming and stirring the suspension in step (b) until the chlorinating agent is completely consumed;

(d) cooling the suspension in step (c);

(e) adding an aniline of formula (IV) dropwise to the suspension in step (d) until the concentration of the aniline is less than about 5%;



(IV)

wherein R_1, R_2, R_3, R_4 and R_0 are as defined above;

(f) adding an aqueous base to the suspension in step (e) to obtain a precipitate; and

(g) filtering and washing and drying the precipitate in step (f) to yield the compound of Formula (II).

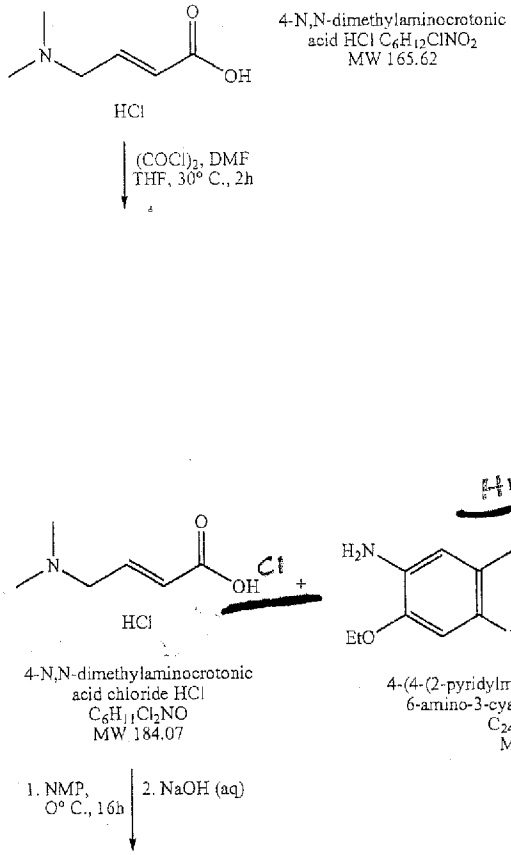
ERROR (3)

For purposes of this invention a heteroaryl comprises a heterocyclic ring system of one to three fused rings, in which at least one ring may have an aromatic character and contains 1 to 4 heteroatoms the same or different selected from the group consisting of S, N, and O. The remaining rings of the ring system may be fully unsaturated, partially saturated, or fully saturated. Each ring comprises three to ten members. Preferred heteroaryl groups are thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, pteridine, carbazole, phenanthridine, acridine, perimidine, phenanthroline, phenazine, phenothiazine, furazan, phenoxazineand pyrrolidine. The heteroaryl can be independently substituted at one or more positions. Preferred substituents are halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, acyl, aldehyde, ester, a cycloheteroalkyl, an aromatic or heteroaromatic moiety, -CN, or Y.

Cycloheteroalkyl as used herein refers to a 5 to 9 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms selected from N, N(C_1-C_6 alkyl), S or O. Preferred cycloheteroalkyl groups are oxolane, thiolane, oxazole, piperidine, piperazine and morpholine. The cycloheteroalkyl can be independently substituted at one or more positions. Preferred substituents are halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a cycloheteroalkyl, an aromatic or heteroaromatic moiety and –CN.

When the heteroaryl is substituted with Y, wherein Y is –NH, -O-, -S-, or –NR-, wherein R is an alkyl of 1-6 carbon atoms, at one position on the ring there is further substitution on the -NH, -O-, -S-, or –NR- with a (CH_2)n-X group. For purposes of this invention n is 0-1 and "X" is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atoms; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with substituents independently selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of

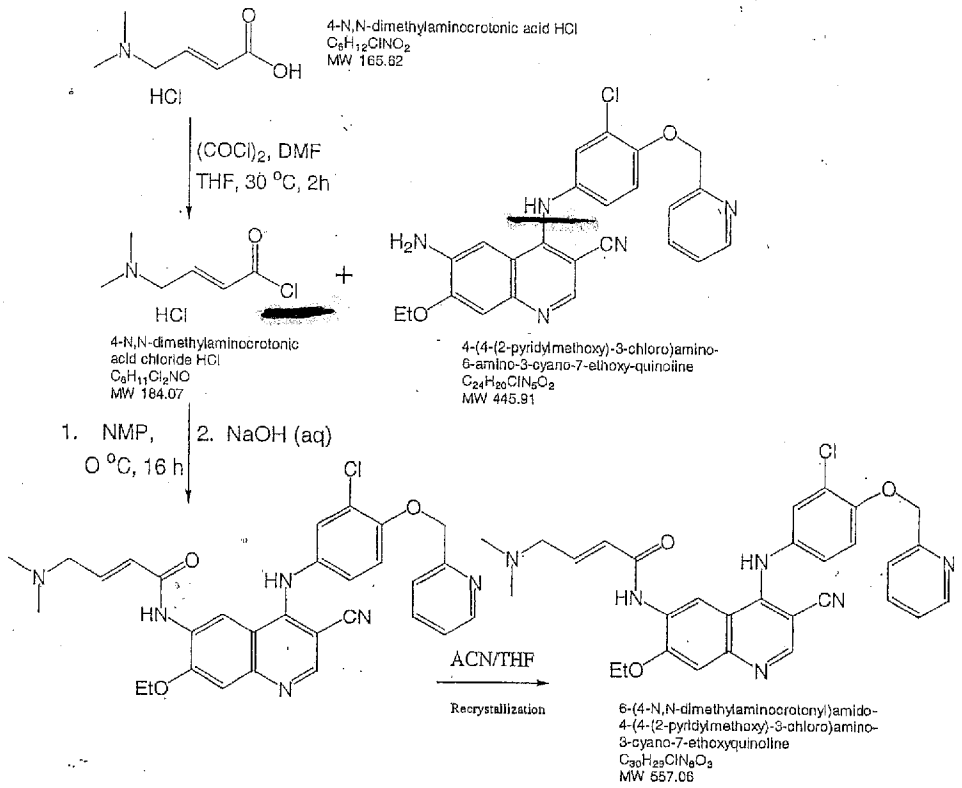
Reaction Scheme Example 2:



A solution of 4-N,N-dimethylaminocrotonic acid hydrochloride in tetrahydrofuran (THF) and a catalytic amount of dimethylformamide (DMF) is cooled to 0–5° C. Oxalyl chloride (0.95 eq) is added dropwise and the mixture warmed to 25–30° C. and stirred until the chlorinating agent is completely consumed. The orange solution is checked for complete consumption of oxalyl chloride by high-pressure liquid chromatography (HPLC) then cooled to 0–5° C. A solution of 4-[4-(2-pyridylmethoxy)-3-chloro]amino-6-amino-3-cyano-7-ethoxyquinoline is added dropwise and the mixture is stirred until ≦0.5% of the starting aniline remains. The reaction is quenched with water and the mixture warmed to 40° C. Aqueous sodium hydroxide is added to bring the pH to 10–11. The resulting precipitates are filtered hot and washed with water. The wet solids are heated to reflux (70–75° C.) in acetonitrile:THF (1:5:1) and the solution cooled slowly to room temperature. The product is filtered and washed with acetonitrile:THF. The product is dried (50° C., 10 mm Hg, 24 hours) to 80–85% yield.

ERROR(S)

Reaction Scheme Example 2:



A solution of 4-N,N-dimethylaminocrotonic acid hydrochloride in tetrahydrofuran (THF) and a catalytic amount of dimethylformamide (DMF) is cooled to 0-5º C. Oxalyl chloride (0.95 eq) is added dropwise and the mixture warmed to 25-30º C and stirred until the chlorinating agent is completely consumed. The orange solution is checked for complete consumption of oxalyl chloride by high-pressure liquid chromatography (HPLC) then cooled to 0-5º C. A solution of 4-[4-(2-pyridylmethoxy)-3-chloro]amino-6-amino-3-cyano-7-ethoxyquinoline is added dropwise and the mixture is stirred until ≤ 0.5% of the starting aniline remains. The reaction is quenched with water and the mixture warmed to 40º C. Aqueous sodium hydroxide is added to bring the pH to 10-11. The resulting precipitates are filtered hot and washed with water. The wet solids are heated to reflux (70-75º C) in

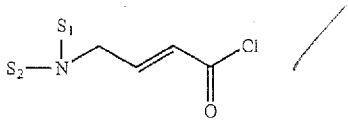
ERROR (8)

mL). The solid is dried under vacuum (~1 torr) at 40–50° C. for 3 hours to give 4.0 g of 4-dimethylaminocrotonoyl chloride hydrochloride. This material is characterized as its methyl ester by treatment of the solid with methanol.

Alternatively, 4-(dimethylamino)-2-butenoyl chloride hydrochloride can be prepared in acetonitrile and used as a suspension in acetonitrile for the next reaction.

What is claimed is:

1. A compound of Formula (I):



(I)

wherein

S_1 and S_2 are each independently, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, aralkyl, substituted or unsubstituted aryl or heteroaryl, or S_1 and S_2 together with the nitrogen to which they are attached form a nitrogen containing heteroaryl or cycloheteroalkyl; or

an acid addition salt thereof.

2. The compound of claim **1** wherein the acid addition salt is a hydrochloride salt.

3. A process for the preparation of a compound of claim **1** comprising:

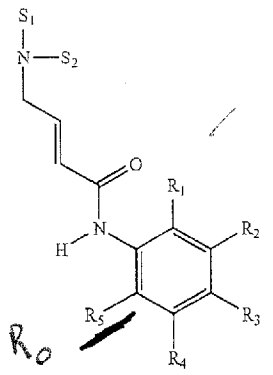
(a) reacting a 4-bromocrotonate with S_1,S_2—N—R wherein R is H, trialkylsilyl or alkali metal and S_1 and S_2 are as defined in claim **1** or an acid addition salt thereof to obtain the corresponding 4-S_1,S_2-aminocrotonate;

(b) hydrolyzing 4-S_1,S_2-aminocrotonate of step (a) in the presence of a base; and isolating as a corresponding hydrochloride salt; and

(c) chlorinating the compound of step (b) with a chlorinating agent to obtain the compound of claim **1**.

4. A process of claim **3** wherein the chlorinating agent is oxalyl chloride.

5. A process for the preparation of a compound of Formula (II):



(II)

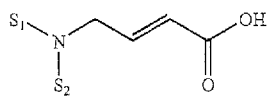
wherein

R_1, R_2, R_3, R_4, and R_0 are independently selected from the group consisting of —CN, alkyl, alkoxy, vinyl, alkenyl, formyl, —CF_3, —CCl_3, halide, —C_6H_5, amide, acyl, ester, amino, thioalkoxy, phosphino, and combinations thereof;

or, taken together, R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_0, together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl or cycloheteroalkyl; and

wherein S_1, and S_2 are defined in claim **1**, comprising:

(a) cooling a suspension of an acid addition salt of the compound of Formula (V);



(V)

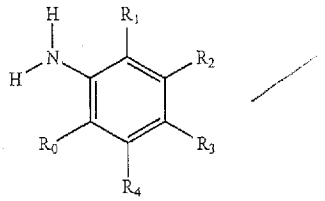
wherein S_1 and S_2 are defined in claim **1**;

(b) adding a chlorinating agent to the suspension in step (a);

(c) warming and stirring the suspension in step (b) until the chlorinating agent is completely consumed;

(d) cooling the suspension in step (c);

(e) adding an aniline of formula (IV) dropwise to the suspension in step (d) until the concentration of the aniline is less than about 5%;



(IV)

wherein R_1, R_2, R_3, R_4 and R_0 are as defined above;

(f) adding an aqueous base to the suspension in step (e) to obtain a precipitate; and

(g) filtering and washing and drying the precipitate in step (f) to yield the compound of Formula (II).

6. The process of claim **5** wherein cooling comprises a temperature of −10 to 25° C.

7. The process of claim **6** wherein the cooling comprises a temperature of 0 to 10° C.

8. The process of claim **5** wherein the warming comprises a temperature of 20 to 30° C.

9. The process of claim **5** wherein the base is selected from sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium bicarbonate, and potassium carbonate.

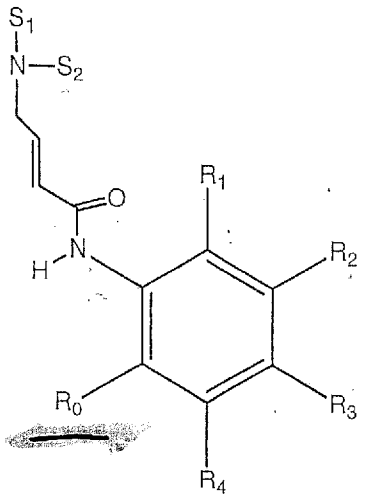
10. The process of claim **9** wherein the base is sodium bicarbonate.

11. The process of claim **5** wherein the aniline is 4-[4-benzyloxy-3-chloro]amino-6-amino-3-cyano-7-ethoxyquinoline, 4-(4-(2-pyridylmethoxy)-3-chloro)amino-3-cyano-7-ethoxyquinoline or [4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxy-quinoline.

12. The process of claim **5** wherein the concentration of the aniline is less than 2%.

* * * * *

ERROR (8)



(II)

wherein

R_1, R_2, R_3, R_4, and R_0 are independently selected from the group consisting of –H, -CN, alkyl, alkoxy, vinyl, alkenyl, formyl, $-CF_3$, $-CCl_3$, halide, $-C_6H_5$, amide, acyl, ester, amino, thioalkoxy, phosphino, and combinations thereof;

or, taken together, R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_0, together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl or cycloheteroalkyl; and

S_1 and S_2 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, substituted or unsubstituted aryl, or S_1 and S_2 together with the nitrogen to which they are attached form a nitrogen containing heteroaryl, comprising:

(a) cooling a suspension of an acid addition salt of the compound of Formula (V);

ERROR (4)

atoms, alkanoyloxymethyl of 2–7 carbon atoms, alkoxy of 1–6 carbon atoms, alkylthio of 1–6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2–7 carbon atoms, carboalkyl of 2–7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1–6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1–6 carbon atoms, alkenoylamino of 3–8 carbon atoms, alkynoylamino of 3–8 carbon atoms, benzoylamino, and —Q—$(CH_2)_m$Ar, wherein Q is selected from O, NH, N(C_1–C_6 alkyl) or S, m is 0, 1 or 2, and Ar is phenyl or pyridyl optionally substituted with one to three moieties independently selected from halogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, azido, hydroxyalkyl of 1–6 carbon atoms, halomethyl, alkoxymethyl of 2–7 carbon atoms, alkanoyloxymethyl of 2–7 carbon atoms, alkoxy of 1–6 carbon atoms, alkylthio of 1–6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2–7 carbon atoms, carboalkyl of 2–7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1–6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1–6 carbon atoms, alkenoylamino of 3–8 carbon atoms, alkynoylamino of 3–8 carbon atoms and benzoylamino.

The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxymethyl, alkanoyloxymethyl, alkylsulphinyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, alkanoylamino aminoalkyl, alkylaminoalkyl, N,N-dicycloalkylaminoalkyl, hydroxyalkyl, and alkoxyalkyl substituents include both straight chain as well as branched carbon chains.

The cycloalkyl portions of N-cycloalkyl-N-alkylaminoalkyl and N,N-dicycloalkylaminoalkyl substituents include both simple carbocycles as well as carbocycles containing alkyl substituents.

The alkenyl portion of the alkenyl, alkenoyloxymethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation.

The alkynyl portion of the alkynyl, alkynoyloxymethyl, alkynylsulfonamido, alkynyloxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation.

For purposes of this invention tri-alkylsilyl applies to alkyl (as hereinbefore defined) derivatives of the silyl group, R_3Si, wherein each R may be the same or different. Preferably, tri-alkylsilyl is trimethylsilyl.

Carboxy is defined as a —CO_2H radical.

Carboalkoxy of 2–7 carbon atoms is defined as a —CO_2R" radical, where R" is an alkyl radical of 1–6 carbon atoms.

Carboalkyl is defined as a —COR" radical, where R" is an alkyl radical of 1–6 carbon atoms.

Alkanoyloxy is defined as a —OCOR" radical where R" is an alkyl radical of 1–6 carbon atoms.

Alkanoyloxymethyl is defined as R"CO_2CH_2 radical where R" is an alkyl radical of 1–6 carbon atoms.

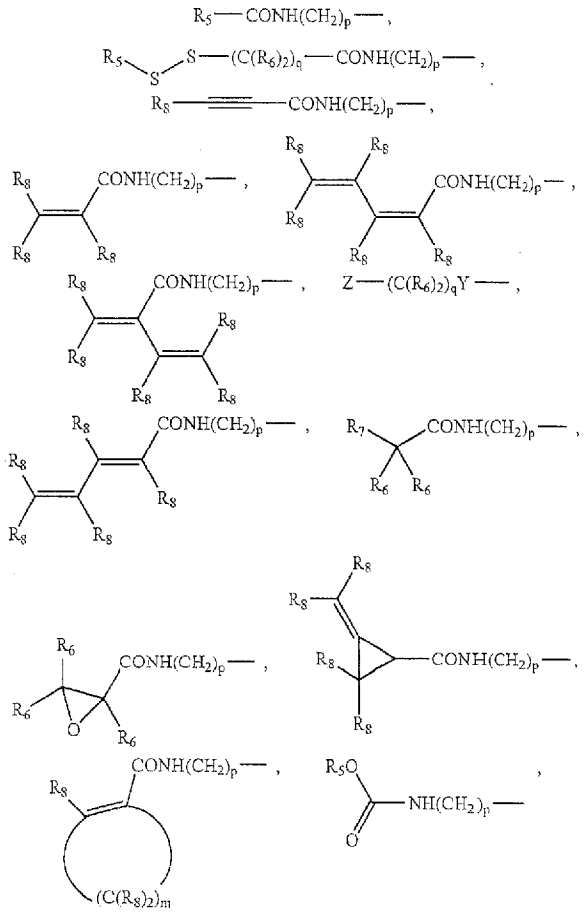
Alkoxymethyl is defined as R"OCH_2 radical where R" is an alkyl radical of 1–6 carbon atoms.

The term "vinyl" is defined as CH_2=CH and derivatives formed by substitution.

"Acyl" is a radical of the formula —(C=O) alkyl or —(C=O) perfluoroalkyl wherein the alkyl radical or perfluoroalkyl radical is 1 to 7 carbon atoms; preferred examples include but are not limited to, acetyl, propionyl, butyryl, trifluoroacetyl.

Alkylsulphinyl is defined as R"SO radical, where R" is an alkyl radical of 1–6 carbon atoms. Alkylsulphonyl is defined as R"SO_2 radical, where R" is an alkyl radical of 1–6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as R'"SO_2NH radical, where R'" is an alkyl radical of 1–6 carbon atoms, an alkenyl radical of 2–6 carbon atoms, or an alkynyl radical of 2–6 carbon atoms. N-alkylcarbamoyl is defined as R"NHCO radical, where R" is an alkyl radical of 1–6 carbon atoms. N,N-dialkylcarbamoyl is defined as R" R'NCO radical, where R" is an alkyl radical of 1–6 carbon atoms, R' is an alkyl radical of 1–6 carbon atoms and R', and R" may be the same or different.

For the purposes of this invention, R_1, R_2, R_3, R_4 and R_0 are each, independently, hydrogen, halogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, alkenyloxy of 2–6 carbon atoms, alkynyloxy of 2–6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1–6 carbon atoms, alkenoyloxy of 3–8 carbon atoms, alkynoyloxy of 3–8 carbon atoms, alkanoyloxymethyl of 2–7 carbon atoms, alkenoyloxymethyl of 4–9 carbon atoms, alkynoyloxymethyl of 4–9 carbon atoms, alkoxymethyl of 2–7 carbon atoms, alkoxy of 1–6 carbon atoms, alkylthio of 1–6 carbon atoms, alkylsulphinyl of 1–6 carbon atoms, alkylsulphonyl of 1–6 carbon atoms, alkylsulfonamido of 1–6 carbon atoms, alkenylsulfonamido of 2–6 carbon atoms, alkynylsulfonamido of 2–6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2–7 carbon atoms, carboalkyl of 2–7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1–4 carbon atoms, alkylamino of 1–6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, aminoalkyl of 1–4 carbon atoms, N-alkylaminoalkyl of 2–7 carbon atoms, N,N-dialkylaminoalkyl of 3–14 carbon atoms, phenylamino, benzylamino,



ERROR (4)

The alkynyl portion of the alkynyl, alkynoyloxymethyl, alkynylsulfonamido, alkynyloxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation.

For purposes of this invention tri-alkylsilyl applies to alkyl (as hereinbefore defined) derivatives of the silyl group, R_3Si, wherein each R may be the same or different. Preferably, tri-alkylsilyl is trimethylsilyl.

Carboxy is defined as a $-CO_2H$ radical.

Carboalkoxy of 2-7 carbon atoms is defined as a $-CO_2R''$ radical, where R" is an alkyl radical of 1-6 carbon atoms.

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The term "vinyl" is defined as CH_2=CH and derivatives formed by substitution.

"Acyl" is a radical of the formula –(C=O) alkyl or –(C=O) perfluoroalkyl wherein the alkyl radical or perfluoroalkyl radical is 1 to 7 carbon atoms; preferred examples include but are not limited to, acetyl, propionyl, butyryl, trifluoroacetyl.

Alkylsulphinyl is defined as R"SO radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as $R''SO_2$ radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as $R'''SO_2NH$ radical, where R"' is an alkyl radical of 1-6 carbon atoms, an alkenyl radical of 2-6 carbon atoms, or an alkynyl radical of 2-6

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 7,126,025

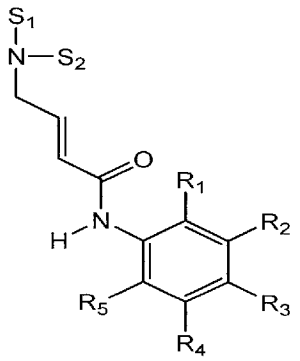
APPLICATION NO. : 10/758,187

ISSUE DATE : October 24, 2006

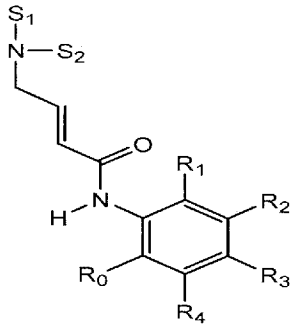
INVENTOR(S) : Considine et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(1) Col. 3, lines 20-34 delete the following structure:



and insert the following structure:



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PATENT NO : 7,126,025

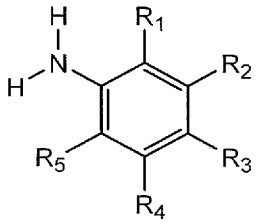
APPLICATION NO. : 10/758,187

ISSUE DATE : October 24, 2006

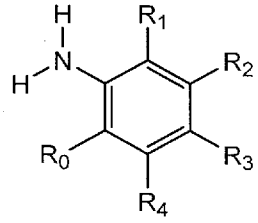
INVENTOR(S) : Considine et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(2) Col. 4, lines 5-14, delete the following structure:



and insert the following structure:



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APPLICATION NO. : 10/758,187

ISSUE DATE : October 24, 2006

INVENTOR(S) : Considine et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(3) Col. 4, line 59, replace " "X" " with -- "X'" -- ;

(4) Col. 6, line 1, replace " R'''SO_2NH radical, where R''' " with -- R'''SO_2NH radical, where R''' -- ;

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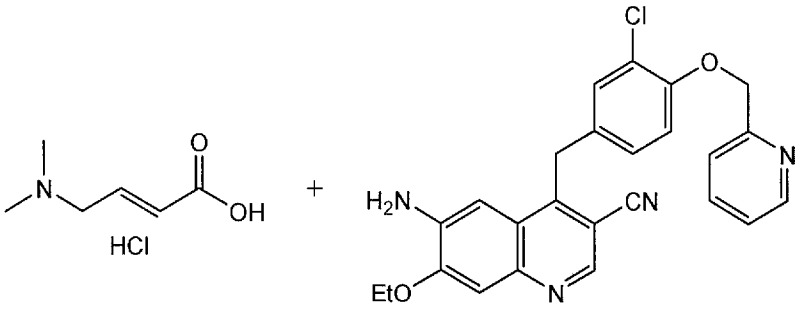
APPLICATION NO. : 10/758,187

ISSUE DATE : October 24, 2006

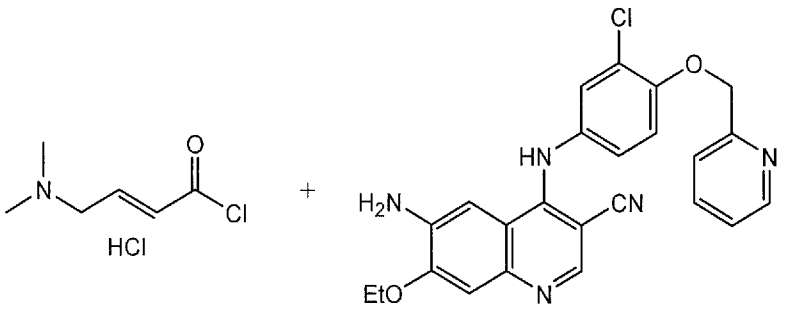
INVENTOR(S) : Considine et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(5) Cols. 13-14, lines 15-35, delete the following:



and insert the following:



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CERTIFICATE OF CORRECTION

PATENT NO : 7,126,025

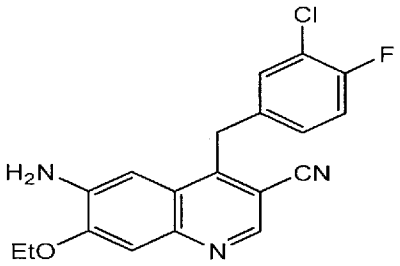
APPLICATION NO. : 10/758,187

ISSUE DATE : October 24, 2006

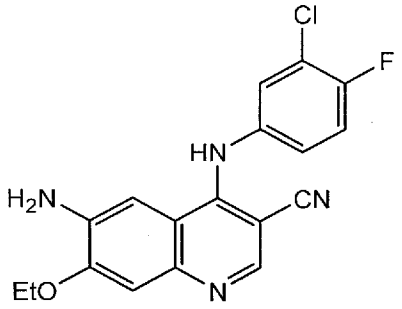
INVENTOR(S) : Considine et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(6) Cols.15-16, lines 15-35, delete the following structure:



and insert the following structure:



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CERTIFICATE OF CORRECTION

PATENT NO : 7,126,025

APPLICATION NO. : 10/758,187

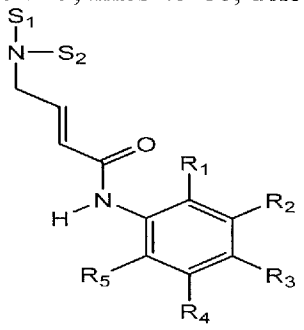
ISSUE DATE : October 24, 2006

INVENTOR(S) : Considine et al

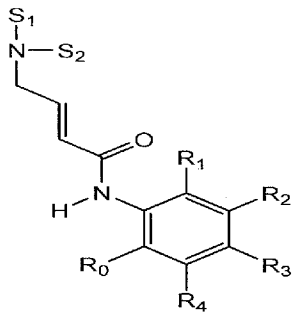
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(7) Col. 20, Line 55, delete the second occurrence of "4-Dimethylaminocrotonic acid

(8) Claim 5, Col. 23, lines 45-60, delete the following structure:



and insert the following structure:



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